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Research letter

Risk of herpes zoster reactivation after messenger RNA COVID-19 vaccination: A cohort study

To the Editor: Recent case series and media coverage suggest an association between receiving the messenger RNA (mRNA) COVID-19 vaccine and reactivation of the varicella zoster virus (VZV).[1-3] Fear of a potential adverse effect will drive vaccine refusal and subsequent preventable disease and death. The purpose of the present investigation is to evaluate the relationship between mRNA COVID-19 vaccination and VZV reactivation.

We performed a retrospective cohort study using the TriNetX Analytics Network (TriNetX, LLC), a federated health research network that aggregates health records from 63 health care organizations comprising 70 million patients. We included patients aged ≥18 years who received the mRNA COVID-19 vaccine either as the first or the second dose between December 15, 2020 and July 15, 2021 (Supplemental Material, available via Mendeley at https://data.mendeley.com//datasets/trkg3zfr5f/1). Herpes zoster reactivation (code B02; International Classification of Diseases, Tenth Edition) related to mRNA COVID-19 vaccine administration was defined as occurring within 28 days.[4]

A control population was established, comprising persons in the database diagnosed with acne, viral wart, melanocytic nevi, dry skin, lipoma, skin cysts, or seborrheic keratosis and who had no history of COVID-19 vaccination (Supplemental Material). Because persons may have received a COVID-19 vaccination at a location outside of the health care organizations participating in the database, we split our control population into 2 cohorts. The first (historical) control cohort comprised individuals who received the aforementioned diagnoses between January 1, 2020 and December 1, 2020 to establish a cohort wherein COVID-19 vaccination was not readily available. A second (contemporary) control cohort comprised individuals diagnosed between December 15, 2020 and July 15, 2021, to parallel study cohort, and to account for possible seasonal variation in VZV incidence.[5] We balanced cohorts using 1:1 greedy nearest neighbor propensity score matching by age, sex, race, ethnicity, HIV status, malignancy, use of antineoplastics, use of immunosuppressants, and receipt of shingles vaccine. Using the matched cohorts, we calculated the relative risk of herpes zoster in the 28 days after index events in the respective cohorts. All statistical analyses were performed within TriNetX.

We identified 1,306,434 persons who received a dose of the mRNA COVID-19 vaccine. The mean age of patients in the mRNA COVID-19 vaccine cohort was 55.1 years (SD, 18.5), 57% were female, 14% were Black, 65% were White, 11% were Hispanic or Latino, and 6% were Asian. Prior to matching, the crude incidence of VZV reactivation within 28 days of mRNA vaccination was 0.1% (1228 of 1,306,434 patients). After 1:1 propensity-matching, demographic and clinical characteristics were balanced (SD <0.1). No difference in VZV reactivation was observed among persons receiving the mRNA COVID-19 vaccine within 28 days compared to both the historical cohort (relative risk, 0.91; 95% CI, 0.82-1.01) and the contemporary cohort (relative risk, 0.98; 95% CI, 0.87-1.11) (Table I).

Table I. Risk of varicella zoster virus reactivation after messenger RNA COVID-19 vaccination

Cohort	Persons in cohort	Persons with VZV reactivation	Risk (per 1000 person-years)*	Risk ratio, 95% CI
mRNA COVID-19 vaccination	555,256	673	16	0.91 (0.82-1.01)
vs historical cohort†	555,256	740	17	
mRNA COVID-19 vaccination	359,789	492	18	0.98 (0.87-1.11)
vs contemporary cohort‡	359,789	501	18	

The relative risk compares the risk of VZV reactivation within 28 days after mRNA COVID-19 vaccination against persons in control cohorts after matching for age, sex, race, ethnicity, HIV, malignancy, use of antineoplastics, use of immunosuppressants, and receipt of shingles vaccine. The diagnoses in the control cohorts were determined upon by authors to be conditions that do not have a known relationship to VZV reactivation. Multiple diagnoses were included to help increase cohort size for robust propensity-matching.

HIV, Human immune deficiency virus; *mRNA*, messenger RNA; *VZV*, varicella zoster virus.

*Risk per 1000 person-years were calculated as followed: (persons with VZV reactivation)/[(Persons in cohort) × (28/365)] × 1000).

†The first (historical) control cohort comprised individuals who received a diagnosis of acne, viral wart, melanocytic nevi, dry skin, lipoma, skin cysts, or seborrheic keratosis between January 1, 2020 and December 1, 2020 and who had no history of COVID-19 vaccination to establish a cohort wherein COVID-19 vaccination was not readily available.

‡A second (contemporary) control cohort comprised of individuals diagnosed between December 15, 2020 and July 15, 2021 to account for possible seasonal variation in VZV incidence.

Herein our data suggest mRNA COVID-19 vaccination is not associated with increased rates of VZV reactivation. We hope this reassures patients and the providers caring for them. Our analysis is limited by potential misclassification bias, which is inherent in the use of diagnostic codes. In addition, persons may have developed herpes zoster, but did not seek care. Lastly, we cannot ascertain the completeness of records, particularly the rates of shingles vaccination.

Morgan Birabaharan, MD,[a] David C. Kaelber, MD, PhD, MPH,[b,c] and Maile Y. Karris, MD[a]

From the Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California, San Diego, La Jolla, California[a]; Departments of Internal Medicine, Pediatrics, and Population and Quantitative Health Sciences, School of Medicine, Case Western Reserve University, Cleveland, Ohio[b]; and Center for Clinical Informatics Research and Education, The MetroHealth System, Cleveland, Ohio.[c]

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Reprint requests: Morgan Birabaharan, MD, Division of Infectious Diseases and Global Public Health, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093

E-mail: mbirabaharan39@gmail.com

Conflicts of interest

None declared.

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